REMARKS

This reply is being filed with a Request for Continued Examination (RCE). Upon entry of the present amendments, claims 1, 3, 7, 8, 17, 18, and 20-33 will be pending. Claims 20-31 are withdrawn. Claims 2, 4-6, 9-16, 19, 32, and 34-37 have been canceled. Applicants have also amended claims 1, 7, and 8. Support for the amendments can be found throughout the specification, for example, at page 2, line 5-6; page 4, line 24; page 17, line 29; and in Examples 2 and 3 at pages 21-23. No new matter has been introduced.

Withdrawn rejections

Applicants note with appreciation that the prior rejections of claims 1, 3, 6-8, 11, 17, and 18 under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) have been withdrawn (Office Action at page 2).

Applicants' Invention

As an initial matter, applicants note that they have proposed to amend the claims, and cancel claims 6, 11, 14, and 34-37 to remove the recitations of a CMV polypeptide that induces a cell-mediated immune response (e.g., pp65), gB, gH, gL and gO, as these are claim features not necessary for patentability. Applicants submit that the claimed compositions are novel and non-obvious because they utilize the combination of gM and gN (i.e., gcII complex) for CMV DNA vaccines. As discussed in more detail below, a combination of gM- and gN-expressing nucleic acid molecules can produce a synergistic neutralizing antibody response that was unexpected, given that either alone produced no or very little response.

35 U.S.C. § 103

The Office rejected claims 1, 3, 6, 17, 32, and 34 as allegedly obvious over Gonczol et al. (US Pat. No. 6,448,389; "Gonczol") in view of Mach et al. (Journal of Virology, 11881-11892, 2000; "Mach") and Temperton (International Journal of Antimicrobial Agents, 19: 169-172, 2002; "Temperton"). Claims 6 and 34 have been canceled.

According to the Office (Office Action at pages 4-5) :

> Gonczol et al, differs from the claimed invention by not teaching a composition comprising of gB, pp65 in combination with gcll (glycoprotein M (gM) complex

> for the development of a HCMV vaccine ... Mach suggests that the gM-gN complex may represent a major antigenic target for antiviral antibody responses and a highly immunogenic structure for the humoral immune response during natural infection ... Mach suggests that future experiments will be directed towards defining the functional and immunological properties of the gM-gN complex ... Temperton teaches that developing a HCMV vaccine is a major public health priority ... One of ordinary skill in the art would have a reasonable expectation of success because the vaccine composition taught by Gonczol and Mach is effective at inducing immune responses in mice.

Applicants respectfully disagree with this rejection and traverse for the reasons set forth below.

The instant claims are directed to a composition including, *inter alia*, nucleic acid molecules comprising nucleic acid sequences encoding the gcII complex. Applicants submit that the Office has failed to establish a *prima facie* case of obviousness because skilled practitioners would not have had a reasonable expectation of success that applicants' composition would work as a DNA vaccine against CMV. Further, even assuming that the Office could present a *prima facie* case of obviousness, the specification sets forth unexpected results that are sufficient to overcome such a case.

The Office has failed to set forth a rational reason to support its conclusion that applicants' composition would have been *prima facie* obvious over Gonczol, Mach, and Temperton. For the sake of argument alone, even assuming that skilled practitioners would have been led to applicants' composition that included nucleic acid molecules comprising nucleic acid sequences encoding the gcII complex (i.e., gM and gN), skilled practitioners would not have reasonably expected that the composition would work as a DNA vaccine against CMV. The Office has not pointed to any evidence dated prior to applicants' filing date showing that any such DNA vaccines would work against CMV. The Office merely concluded that there was such an expectation because "the vaccine composition taught by Gonczol and Mach is effective at inducing immune responses in mice." (Office Action at page 6). However, such conclusion is not supported by the teachings of the references.

As acknowledged by the Office (Office Action at pages 4-5), Gonczol does not even mention the gcII complex, much less provide a reason to conclude that a DNA vaccine including nucleic acid molecules encoding the gcII complex would work. Further, contrary to the Office's assertion, applicants fail to find any mention in Mach of any composition being administered to

mice, or any other animal models. Mach suggests that gM and gN form a complex, and that the complex may be an antigenic target of antiviral antibody responses. However, there is nothing here to imply that a DNA vaccine against CMV based on gM and gN would be successful, and in fact, Mach makes no reference to any DNA vaccines. Neither does Temperton rectify the deficiencies of Gonczol and Mach. The Office only cites the publication for suggesting the importance of developing vaccines against CMV. In any event, the only reference to gM and gN in Temperton is what is already disclosed in Mach (see page 169, right column, the end of the first paragraph). Thus, there is nothing in Temperton that would have led skilled practitioners to expect that applicants' composition would be successful as a DNA vaccine against CMV. Applicants fail to see how the Office arrived at the conclusion that a reasonable expectation of success existed given the complete lack of supporting evidence.

Moreover, as pointed out by the Office (Office Action at page 5), "Mach suggests that future experiments will be directed towards defining the functional and immunological properties of the gM-gN complex." In other words, the biological properties of the gcII complex were not understood, even in view of Mach, the only one of the three cited references that provides any information at all about the gcII complex. The Office has not pointed to anything else that would supplement the teachings of Gonczol, Mach, and Temperton regarding gcII. Therefore, reading these references, in combination or individually, skilled practitioners would not have reasonably expected that a composition including nucleic acid molecules comprising nucleic acid sequences encoding the gcII complex would work as a DNA vaccine against CMV. Accordingly, the Office has failed to establish a *prima facie* case of obviousness against claims directed to a composition including nucleic acid molecules comprising nucleic acid sequences encoding the gcII complex.

Even if the Office could establish a *prima facie* case of obviousness, applicants have presented surprising results in their application sufficient to overcome such a case of obviousness. As stated in the specification (at page 21, line 29, to page 22, line 18):

> 293T cells were transiently tranfected with a gM and gN-encoding DNA vaccine plasmid ... This experiment shows that co-expression of DNA encoding both gM and gN resulted in higher levels of expression than observed when either glycoprotein was expressed alone ... Co-administration of gM- and gN-expressing nucleic acids may permit optimal expression of these gene products,

> leading to potent stimulation of an immune response against the antigens. Furthermore, providing these antigens via DNA vaccination eliminates the complications of preparing proteins for administration. This is particularly useful for proteins such as these, which are membrane-associated and form complexes during biosynthesis in the cell, and thus would be expensive to express, purify, and administer in protein form.

Thus, it was unexpected that co-administration of nucleic acid molecules encoding gM and gN would lead to optimal expression of these antigens. Consequently, there are unexpected advantages to providing gM and gN as a DNA vaccine. Furthermore, the specification also states (at page 22, line 30, to page 23, line 4; emphasis added):

> As seen in Table 1, while the gM vaccine alone was able to induce low titer neutralizing antibody in the immunized rabbit (and gN alone had been shown to be ineffective), the combination of gM and gN (gM/N) was able to induce a much higher, and greater than additive (synergistic), neutralizing antibody response. A higher neutralizing titer is reflected in the fact that virus was neutralized by a greater dilution of serum from gM/N-vaccinated rabbits as compared to rabbits vaccinated with gM alone.

Hence, a combination of gM- and gN-expressing nucleic acid molecules can produce a synergistic neutralizing antibody response that was unexpected, given that either one alone produced no or very little response. Applicants submit that such unexpected results are sufficient to rebut any alleged *prima facie* case of obviousness, if indeed such a case could be established.

In view of the foregoing, applicants submit that claims 1, 3, 6, 17, 32, 34 are not obvious over Gonczol, Mach and Temperton, individually or combined. Reconsideration and withdrawal of this rejection are respectfully requested.

The Office also rejected claims 7-8, 11, 14, 18, 33, 36, and 37 as allegedly obvious over Gonczol in view of Mach, Temperton, Theiler et al. (Journal of Virology, 2890-2898, 2002; "Theiler") and Weiss et al, (Vaccine, 18: 815-824, 2000; "Weis"). Claims 11, 14, 36, and 37 have been canceled.

The Office Action states (at pages 7-9):

> Gonczol/Mach/Templeton do not teach a HCMV vaccine with inclusion of HCMV gclll immunogenic composition ... Theiler is an exemplified prior art that teaches the gclll (gH and gL and gO) complex is necessary for the final stage of the virus entrypH-independent fusion of the viral envelope with the host cell plasma membrane ... Gonczol/Mach/Templeton/ Theiler do not teach HCMV

> vaccine with the truncated form of gB in association with a tissue plasminogen activator leader sequence ... Weiss teaches that immunization with the construct containing the OspC gene undr the transcriptional control of the CMV promoter elicited a marginal response, which was drastically improved by a fusion construct containing the human tissue plasminogen activator leader sequence ...

Applicants disagree and traverse for the reasons set forth below.

Claim 7 and its dependent claims all recite a composition including, *inter alia*, nucleic acid molecules comprising nucleic acid sequences encoding gM and gN. As set forth above, such a composition is not obvious over Gonczol, Mach, and Temperton, given that skilled practitioners would have had no expectation of success and that there are surprising results sufficient to rebut a *prima facie* case of obviousness. Thus, these claims are not obvious over Gonczol, Mach, and Temperton for at least the same reasons.

Theiler does not remedy the deficiencies of Gonczol, Mach and Temperton, especially in view of the presently proposed claim amendments. The Office cites Theiler for disclosing that "... the gclll (gH and gL and gO) complex is necessary for the final stage of the virus entrypH-independent fusion of the viral envelope with the host cell plasma membrane." However, Theiler in its entirety is focused on the post-translation processing and trafficking of gO in cells (see e.g., Title, Abstract, and Discussion). These concepts are not relevant to the claims as presently amended. There is nothing in the reference about DNA vaccines against CMV or even using gcIII as a target to develop any types of vaccine. Certainly, there is no mention of gN, gM, or gcII. As such, Theiler does not provide anything that would have led skilled practitioners to a composition including nucleic acid molecules comprising nucleic acid sequences encoding gM and gN. Further, since there is nothing about DNA vaccines, Theiler fails to provide a reason to expect that any DNA vaccines would work against CMV. Thus, Theiler fails to supply any information that would render the instant claims obvious, even in view of Gonczol, Mach and Temperton

Weiss does not rectify the deficiencies of Gonczol, Mach, Temperton, and Theiler. The Office cites Weiss for disclosing a construct containing the OspC gene fused to a human tissue plasminogen activator leader sequence. The publication fails to say anything about CMV DNA vaccines, gN, gM, or gcII. In fact, it is not even about a virus, but rather the bacteria *Borrelia*. Thus, applicants fail to understand why skilled practitioners would have been led to combine

Weiss with Gonczol, Mach, Temperton and/or Theiler in the first place. Even if skilled practitioners were to combine these references, they still would not have arrived at applicants' claimed compositions, as Weiss provides nothing that would remedy the deficiencies in the teachings of the other four references regarding DNA vaccines against CMV, gN, gM, or gcII.

Accordingly, the instant claims are not obvious over Gonczol, Mach, Temperton, Theiler and Weiss, individually or in combination. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Office further rejected claims 1, 34, and 35 as allegedly obvious over Gonczol, in view of Mach, Weiss, and Endresz et al. (Vaccine 17: 50-58, 1999; "Endresz"). Claims 34 and 35 have been canceled. According to the Office (Office Action at pages 9-10): "Gonczol/Mach/Weiss differs from the claimed invention by not teaching a composition, wherein the gB expresses a truncated form of gB in association with a tissue plasminogen activator leader sequence ... Endresz teaches that the HCMV gB secreted form is more immunogenic than the membrane-bound full-length gB..." Applicants disagree and traverse for the reasons stated below.

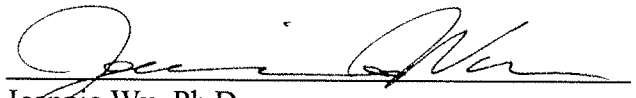
As noted above, claim 1 is directed to a composition including, *inter alia*, nucleic acid molecules comprising nucleic acid sequences encoding the gcII complex (i.e., gM/gN). The composition is not obvious over Gonczol, Mach, and Weiss for at the reasons set forth above. Endresz does not remedy the deficiencies of these references. The Office cites Endresz for teaching a composition having a plasmid that expresses gB and pp65. This information does nothing to lead skilled practitioners to applicants' claimed compositions comprising nucleic acid molecules having nucleic acid sequences encoding the gcII complex. Further, as there is nothing in Endresz about the gcII complex, reading the reference, skilled practitioners would not have reasonably expected that applicants' composition would work as a vaccine against CMV. Applicants, therefore, submit that these references, individually or combined, do not render applicants' composition obvious. Thus, withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants respectfully request that all claims be allowed. Applicants do not concede any positions of the Examiner that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims. The fees for a two-month extension and an RCE in the total amount of $635.00 are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-190001.

Respectfully submitted,

Date: July 18, 2008



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